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EXAMINER	
ALLEN, MARIANNE P	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,692	MELTON ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 41-44* is/are pending in the application.

4a) Of the above claim(s) *41-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26 and 41-44* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-26, in the reply filed on 2/15/06 is acknowledged. The traversal is on the ground(s) that there is no burden of search. This is not found persuasive because burden of search has been previously established in part due to the necessity of a non-coextensive non-patent literature search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 41-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/15/06.

Claim Objections

The disclosure is objected to because of the following informalities:

The claims and the specification contain several typographical errors. Some of the misspellings include ciliary, Schwannoma, Schwann, and serotonergic. It appears that "stiatal-derived" may be intended to be "striatal-derived" but this is not clear. (See for example claim 24.)

Claim 25, line 3, recites "said said." It appears that one of these should be deleted.

Appropriate correction is required.

Specification

The substitute specification submitted 11/25/03 has been entered. The requirement for a new oath will be withdrawn in view of applicant's remarks in the response submitted 2/16/06.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18, 21, and 25-26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,686,198. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of inducing differentiation to a neuronal phenotype with overlapping embodiments.

Claim Rejections - 35 USC § 112

Claims 1-21 and 25-26 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the specific embodiments of the methods exemplified in the specification (Examples 1-19). See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification demonstrates that when capped sense RNA for a truncated activin receptor lacking the cytoplasmic domain, is injected into a two-cell embryo, neural tissue is induced from cells that normally do not differentiate to neural cell types. Injection of RNA encoding the wild-type activin receptor can rescue these embyros. Injection of RNA for Xenopus follistatin (XFS-319) into embryos also induced neural tissue without mesoderm induction. The follistatin protein is secreted by the cells. The specification states that rat inhibin and follistatin also worked in Xenopus embryos. The specification does not appear to specifically identify the type of embryos used in the examples but it appears from context that these must have been Xenopus (frog) embryos.

It is noted that the preamble of claim 1 implies that contacting the cell with the antagonist induces a cell to differentiate to a neuronal cell phenotype; however, the body of the claim has no step or requirement for development of such a neuronal phenotype. In the absence of such a step, antagonism could simply block differentiation to a non-neuronal phenotype without inducing any neuronal phenotype. As such, the methods as claimed would not necessarily result in the effect set forth in the preamble. Similarly, the body of claim 25 has no step or requirement for differentiation along a determined neuronal pathway.

The claimed methods are enabled for the specific situations set forth above (Xenopus two cell embryos, follistatin, inhibin, the truncated activin receptor, injection of RNA etc.).

However, the remaining methods encompassed by the claims are not enabled by the specification and are deemed to constitute an invitation to experiment. The methods as claimed require one to experimentally determine every parameter of the method in order to practice the invention. This greatly exceeds routine experimentation.

The claimed methods require that one know the identity of growth factors from the TGF-β family that normally induce a cell to differentiate to a non-neuronal phenotype. However, the specification identifies only the TGF-β family growth factors activin and Vg-1 and their action upon Xenopus embryos or cells. It is not known what other TGF-β family growth factors have this biological effect or those cells in which this effect occurs. It is not known what other cells activin and Vg-1 have this biological effect upon. It would require undue experimentation to determine other growth factors and the corresponding cells that can be induced to differentiate to a non-neuronal phenotype in the absence of additional guidance.

The claimed methods also require that one know the identity of agents that antagonize the biological action of the aforementioned growth factor. The agents are not limited to proteinaceous agents in the broad claims. Only a few proteinaceous antagonists of activin are identified by the specification. These all antagonize by binding activin. In the case of the truncated activin receptor, activin is bound but the receptor is dysfunctional and cannot transduce a signal. It is not known what the antagonists of Vg-1 are. It is not known what other agents can antagonize the action of activin. It would constitute undue experimentation to determine other antagonists in the absence of further guidance. With respect to antisense nucleic acid constructs (see claim 12), the specification identifies no sequences that would be expected to have the desired effect. Antisense technology is not deemed to be predictable and the specification provides no guidance on which genes an antisense oligonucleotide would be directed against in order to achieve the desired effect. With respect to disrupting a signaling pathway (see claim

26), the specification does not provide sufficient guidance on the mechanism of signaling to permit one to disrupt the pathway other than by inhibiting binding to the activin receptor or introducing a dysfunctional activin receptor. That is, disrupting the pathway at other points in the cascade is not enabled.

Many of the claimed methods require that one further know that an appropriate receptor for the aforementioned growth factor is present on the cell surface. The specification identifies only activin receptors as being present in Xenopus embryo cells. The specification and prior art of record do not establish that any other TGF-β family receptors or other receptors are present in Xenopus embryos or any of the other particular cell types recited in the claims. Growth factors may bind to multiple receptors and it is not known which receptors would be required to be present. For example, it would constitute undue experimentation to determine if activin would bind to an inhibin receptor and cause the desired effect.

The examples of the specification provide no basis upon which to predicate success of the method on other cell types or organisms. Xenopus cells are not predictive of mammalian cells. Undifferentiated two-cell stage embryos are not predictive of terminally differentiated neuronal cells, fetal cells, and neonatal cells, for example. In addition, the specification does not identify any terminally differentiated neuronal cells that can be induced to a non-neuronal phenotype by a TGF-β family growth factor which could then be induced to develop a second neuronal cell phenotype in response to the antagonist. (See claims 19-20.) The specification does not correlate and the art of record does not recognize the Xenopus embryo system as a model system of or predictive for mammals or other species. Particularly, the specification does not establish that it would be predictive of in vivo results in at least mammals.

It is noted that the examples of the specification administer RNA encoding the agent that antagonizes by injection to the cells. Example 12 administers conditioned medium to animal

caps that exerts the desired effect; however, the specification does not identify the agent(s) in the conditioned medium that produces this effect. It is not known if the effect is due to a particular protein or combination of proteins or due to some other cause. It is not considered that injection of RNA to a cell is correlated or predictive of effects caused by direct administration of proteinaceous or non-proteinaceous agents directly. The specification does describe administration of proteins or other agents directly. Direct administration to even a Xenopus embryo in vitro could not be predicted to be successful because the protein or other agent may not be accessible to the intended cell.

In addition, the examples do not support methods using dissociated cell cultures or in isolated single cells. The Xenopus embryos used clearly demonstrate that the total environment of the organism (interaction of all cells and intact intercellular communication) is required to cause the desired effect.

The following references support the above positions.

Melton (Science, 1991) indicates that competence to respond to inducers is transient. (See page 238, right column.)

Hemmati-Brivanlou et al. (Nature, 1992) indicates that induction studies in vertebrates other than frogs would be required to show whether results were generally applicable. (See page 614, right column.)

Sokol et al. (Developmental Biology, 1992) indicates that the relevance of the effects of injection of mRNA into the early Xenopus embryo are uncertain with respect to in vivo inductive interactions. (See page 348, left column.)

Gurdon (Cell, 1992) indicates that pattern development in mammals differs from other animals.

Lemaire (Nature, 1992) indicates in commentary to a reference by the inventors that mutant mice lacking potential endogenous factors or their receptors would provide conclusive evidence that individual molecules are involved in induction. (See page 586, right column.)

Hemmati-Brivanlou et al. (Cell, 77(2):273-281, 1994) indicates that it is speculation that the default state of all embryonic cells is neural and that evolutionary conservation of the general strategy of generating neural fate by inhibition of other embryonic fates has occurred. (See pages 278-279.)

Mather et al. (Endocrinology, 1993) discloses adding activin followed by neutralizing antibodies to activin to germ-Sertoli cell co-cultures. The reference is silent as to whether activin causes these cells to differentiate to non-neuronal phenotypes and whether addition of antibodies results in induction of these cells to neuronal phenotypes. It is noted that activin binding proteins other than the antibodies for activin had differential effects. (See page 2733, right column.) It does not appear from the reference that differentiation of these cells occurs in either case. If this is correct, it provides evidence that many methods encompassed by the claims are inoperable. Alternatively, if activin does cause germ-Sertoli cells to differentiate to non-neuronal phenotypes and the antibodies result in induction to neuronal phenotypes, then this reference would be anticipatory. (See also art rejections below.)

The specification itself at pages 6-7, bridging paragraph, alludes to the fact that all TGF-β family growth factors may not inhibit neuralization.

With respect to claims 6 and 10-11, the specification identifies only a single truncated activin receptor that has the requisite activity. This receptor has not been sufficiently characterized by the specification so as to permit mutation without undue experimentation. It is not known which amino acids would be required to disrupt to cytoplasmic signaling of the

receptor sufficient to have the desired effect. Likewise, mutations to other agents are not enabled as these proteins are not sufficiently characterized.

With respect to claim 15 and 23-24, "a nerve growth factor," "glial growth factor," and "Schwannoma-derived growth factor" do not identify specific growth factors and the metes and bounds of these second growth factors cannot be determined. It is not known what a "stiatal-derived growth factor" is. The metes and bounds of a "growth factor having neurotrophic activity" do not appear to be set forth in the specification.

With respect to claims 17-18, the specification does not enable how to identify specific neural progenitor cells in order to determine if the limitation of the claims has been met. That is, is a fertilized egg considered the ultimate progenitor cell because all cells in the organism originate from this cell or is the cell that immediately precedes the desired phenotype considered the phenotype?

With respect to claim 20, it is not known what the metes and bounds of a "peptidergic cell" are. All cells, not only terminally-differentiated neuronal cells, produce proteins.

For all of these reasons, it is considered to constitute undue experimentation to practice the invention as claimed. The specification is deemed to constitute an invitation to experiment, particularly with respect to isolated single cells, dissociated cell cultures, mammalian cells and organisms.

Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

The preamble of claims 22-24 indicates that contacting the cell with the antagonist results in prevention of death of a neuronal cell. There is no limitation in claims 22-24 that a neuronal phenotype must result from administration of the antagonist although the preamble would imply this. It is noted that the body of the claim has no step or requirement for preventing cell death. As such, the methods as claimed would not necessarily result in the effect set forth in the preamble.

The specification does not demonstrate that cell death (generally or specifically) results in the absence of administration of the recited antagonist. Rather the cells will differentiate along their normal path. Nor do the examples demonstrate that the neuronal cells that may result by administering the antagonist do not die due to the absence of other required factors or by programmed cell death in further development of the Xenopus embryo, for example. The examples of the specification do not appear to address cell death in any respect. As such, the specification is not deemed to support or enable any aspect of these claims.

Should these issues be overcome, most of the issues set forth above in the enablement rejection of claims 1-21 and 25-26 would also apply to these claims.

Claims 6, 9-10, 15, and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is confusing in reciting "truncated activin receptor." Claim 5 requires that the truncated receptor comprise a soluble growth factor-binding domain but claim 6 does not clearly include this limitation. The truncated receptor of claim 6 could be interpreted not to include this domain. The scope of the claim cannot be determined.

Claim 9, line 4, recites "activin" but there is no antecedent basis in claim 7 for this term.

Claim 10 is confusing in reciting "TGF-β polypeptide is a mutated activin." It is not clear if this is in reference to the antagonizing agent defined in claim 9 or the polypeptide growth factor that normally induced cell differentiation to a non-neuronal phenotype of claim 1.

Claims 15 and 24 recite "such as" in line 2. The claim does not clearly indicate that the suggested proteins are limitations of these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 17, 21-23, and 25-26 are rejected under 35 U.S.C. § 102(a) as being anticipated by Fukui et al. (Developmental Biology, September 1993).

Fukui et al. discloses adding Xenopus follistatin protein to ectoderm sheets of the late blastula of Xenopus. When added in the presence of Xenopus activin-AB, mesoderm induction

was suppressed or inhibited. (See Table 1; Figure 7; pages 136-137, bridging paragraph; and page 138, left column.)

The single method step of claims 1, 22, and 25 is contacting a cell that normally differentiates to a non-neuronal phenotype in the presence of a particular protein with an agent that antagonizes the activity of this protein. Fukui et al. discloses such a method step by adding follistatin, an antagonizing agent, to cells of an ectoderm sheet. These cells normally are induced to differentiate to mesoderm by activin.

With respect to claims 2-3, follistatin is known to bind to activin and thus would sequester or keep activin from binding to its cellular receptor.

With respect to claims 17 and 21, ectodermal cells are deemed to meet the limitation of neural progenitor cells and embryonic cells, respectively.

Thus, the method of Fukui et al. is deemed to anticipate the claimed methods because all of the method steps are disclosed.

Claims 1-4, 22-23, and 25-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Yamada et al. (Biochemical and Biophysical Research Communications, August 1992).

Yamada et al. discloses adding activin and follistatin proteins to a human myelocytic cell line, HL-60. Administration of activin-A alone caused differentiation of these cells into monocyte/macrophage-like cells (non-neuronal phenotypes.) Addition of follistatin caused dose-dependent inhibition of differentiation. (See abstract; pages 82-83, bridging paragraph.)

The single method step of claims 1, 22, and 25 is contacting a cell which normally differentiates to a non-neuronal phenotype in the presence of a particular protein with an agent that antagonizes the activity of this protein. As above, the method of Yamada et al. is deemed to anticipate the claimed methods because all of the method steps are disclosed.

Claims 1-4, 22-23, and 25-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hashimoto et al. (Journal of Biological Chemistry, April 1992).

Hashimoto et al. discloses addition of follistatin to various neural cell lines which stimulated neural differentiation. Addition of activin to these cells did not result in neural differentiation but rather inhibited it. (See abstract; pages 7204-7205, bridging paragraph; Figure 1B.)

The single method step of claims 1, 22, and 25 is contacting a cell which normally differentiates to a non-neuronal phenotype in the presence of a particular protein with an agent that antagonizes the activity of this protein. As above, the method of Hashimoto et al. is deemed to anticipate the claimed methods because all of the method steps are disclosed.

Should applicant argue that Fukui et al., Hashimoto et al., and Yamada et al. do not teach differentiation to a neuronal cell phenotype, prevention of death of a neuronal cell, and/or differentiation along a determined neuronal pathway as set forth in the preambles to the claims, this will be construed as an admission that the claims are incomplete and do not recite sufficient steps and/or conditions as well as an admission that the scope of the methods as claimed is not enabled by the specification because it would have been unpredictable as to which cells, growth factors, antagonizing agents, means of contacting (e.g. in form of protein or by injection of nucleic acid), and amounts of antagonizing agents would result in the desired effect.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Thursday, 5:30 am - 1:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne P. Allen
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mpa